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Two mutually complementary synthetic approaches towards 3-substituted 3,4-disubstituted and 1-(2-pyridyl)-substituted isoquinolines

Two mutually complementary synthetic approaches towards 3- and 3,4-disubstituted 1-(2-pyridyl) isoquinolines were studied. The aryne-based method was successfully used for the obtaining of the corresponding the 3-cyano-1-(2-pyridyl)isoquinolines in one step/pot reaction, while it is unacceptable for the obtaining of other 1-(2-pyridyl)isoquinolines. The enamine-based approach was successfully applied for the synthesis of other 1-(2-pyridyl)isoquinolines, while it was unacceptable for the obtaining of 3-cyano-1-(2-pyridyl)isoquinolines.

Keywords: 1,2,4-triazines; arynes; enamines; isoquinolines; aza-Diels-Alder reaction; domino-transformation.

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Results and Discussion

Aryne intermediates, generated *in situ*, are currently attracting more and more attention from the point of view of their use in organic synthesis, since practically useful products of various purposes can be obtained [1–3]. Recently, we have demonstrated the possibilities of their successful use in reactions with substituted 1,2,4-triazines for obtaining both the expected aza-Diels-Alder reaction products, namely the corresponding isoquinolines, and the domino transformations, for example, 10-(1*H*-1,2,3-triazol-1-yl)pyrido

[1,2-*a*] indoles. The direction of the reaction depends on the nature of the 1,2,4-triazines (or arynes) introduced into the composition of the substituents [4].

This article analyzes the two synthetic approaches we have developed for the synthesis of 1-(2-pyridyl) isoquinolines with different substituents in the C3 and C4 positions, which are of interest, in particular, as ligands for transition metal cations [5], as well as from the point of view of creating OLED [6].

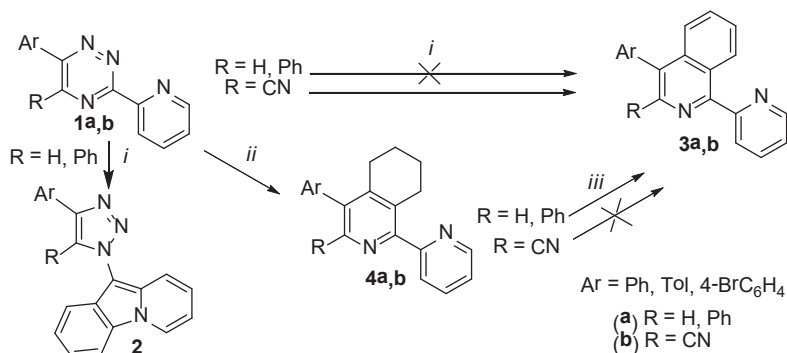
Thus, the reaction of 3-(2-pyridyl)-1,2,4-triazines **1a**, having an aromatic substituent or a hydrogen atom at the C5 position, with aryne results in the corresponding pyrido [1,2-a] indoles **2** [7] (scheme 1), while the synthesis of target 1-(2-pyridyl) isoquinolines **3a** in this way is impossible. To solve this problem, we developed an alternative synthetic approach, which was based on the use of 3-(2-pyridyl)-1,2,4-triazines **1** as starting compounds. The approach involves the preparation of 5,6,7,8-tetrahydroisoquinolines **4a** as a result of the reaction of aza-Diels-Alder (Boger) with enamine followed by oxidative aromatization of the isoquinoline system [8]. 1-Morpholinocyclohexene was used as a dienophile for the first stage. Subsequent aromatization using DDQ as an oxidizing agent made it possible to successfully synthesize isoquinolines **3a**.

It should be noted that in the reaction of 3-(2-pyridyl)-1,2,4-triazine-5-carbonitriles **1b** with arynes, the corresponding isoquinolines **3b** were also obtained as main products, whereas the products of domino transformation were the minor products (the yield is not more than 3%) [9].

We also investigated the possibility of obtaining isoquinolines **3b** as a result

of two-stage synthesis through the preparation of tetrahydroisoquinolines **4b**. The first step was performed by the same procedure as in the case of synthesis **4a**, and afforded the compound **4b**. However, subsequent aromatization of tetrahydrocyanoisoquinoline under various conditions, such as boiling in *o*-xylene or 4-chlorotoluene with oxidants, such as DDQ or chloranil, as well as prolonged boiling in the same high-boiling solvents in the presence of Pd/C did not lead to the formation of the desired isoquinolines **3b**. In all cases the initial tetrahydroisoquinoline **4b** was isolated. Thus, the application of this method is not acceptable for the obtaining the target 3-cyanoisoquinolines **3b**.

Thus, it was demonstrated that two mutually complementary synthetic methodologies can be used to synthesize 3-aryl-, 3,4-diaryl-, as well as 3-cyano-1-(2-pyridyl)isoquinolines. Thus, in the case of R = CN (Scheme 1), the synthesis using aryne intermediates makes it possible to efficiently obtain the corresponding isoquinolines **3b**, while the method based of the preparation tetrahydroisoquinolines **4b** does not allow this because of the impossibility of subsequent aromatization by using the common methods. At the same time, in the



Scheme 1. Reagents and conditions: i) Anthranilic acid, isoamyl nitrile, toluene — 1,4-dioxane (4: 1), boiling, 1.5 h; ii) 1-morpholinocyclohexene, without solvent, 200 °C, 4 h; iii) DDQ, *o*-xylene, 143 °C, 10 h

case of R = H or Ar, the opposite situation is observed: the synthesis of isoquinolines **3a** is possible with the use of a two-step pathway by using the corresponding enam-

ine, and in the case of using aryl intermediates, the reaction leads mainly to rearrangement products **2**.

Experimental

NMR ^1H and ^{13}C spectra were recorded on the spectrometer "Bruker-Avance-400" (400 MHz), internal standard is SiMe_4 . The melting points were measured on the "Boetius" device. Mass spectra (type

of ionization is electrospray) were recorded on the device of series "MicroTOF-Q II" of "Bruker Daltonics" (Bremen, Germany). Elemental analyses were performed on CHN analyzer PE 2400, series II by Perkin Elmer.

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